

Fine Chemicals

COVER STORY

service capabilities. But more acquisitions by Indian firms are expected, and the core custom API market in Europe and North America is coming under threat. Rhodia's recently announced sale of its Rhodia Pharma Services (RPS) custom pharma intermediates business to Shasun will not be the last deal of its kind, industry experts say.

India's contract manufacturing sector will increase its sales from \$100 million in 2005, to \$1 billion in 2010, says investment broker Motilal Oswal Securities (Mumbai) in a recent report. All of the leading low-cost Asian CMOs "are going for the API business in the West," says Girish Malhotra, president of pharma consulting firm EPCOT International (Pepper Pike, OH). "They are making significant inroads into the U.S. API market," Malhotra says.

LOW-COST BASE. Companies such as NPIL are approaching the international API market from a relatively low cost base, and in many cases firms from a number of Asian countries are practicing more efficient chemistry and manufacturing processes than their European and American counterparts, Malhotra says.

Roche's production process for the antiviral drug Tamiflu, used to treat human flu and possibly bird flu, is an example, he says. Roche says that production of the drug is highly complex and that it has taken about a year to commercialize. However, generic drugs firm Cipla (Mumbai) says that over the last few months it has developed a new process for Tamiflu that it expects will squeeze commercialization time to three months, and that it hopes to gain FDA approval for the process within weeks. "In the West, in one unnamed case, a pharma company has been using a process with a 14% product yield," Malhotra says. "Even 50% yield processes today should be unacceptable, but are in use in the West. Indian companies are beating them hands down."

FDA is striving to develop a more efficient approach to chemistry, and will increasingly favor Indian CMOs, Malhotra says. "Improving the foundation of manufacturing science in our current manufacturing practices should be the primary basis for moving away from the corrective-action 'crisis' to continuous improvement," FDA says in a recent report.

Indian CMOs' strategy to increase their share of overseas API markets will likely be underpinned by major pharma companies such as Pfizer and Merck & Co., which are striving to reduce manufacturing costs by billions of dollars, some experts say. Major

Indian Firms Tear Into Overseas API Markets

Indian custom fine chemical contract manufacturing organizations (CMO) are no longer satisfied with increasing their share of the pharmaceutical intermediates market and have started to target the high-value, high-tech active pharma ingredient (API) sector, which until now was served only by European and North American competitors including BASF, Cambrex, and Degussa. Indian firms such as Dr Reddys Laboratories (DRL;

Hyderabad), Nicholas Piramal India Ltd. (NPIL; Mumbai), and Shasun Chemicals and Drugs (Chennai) have in recent months made what they consider to be key API acquisitions overseas. They expect these acquisitions to be a springboard to building an overseas presence in high-tech API manufacturing sectors such as high-potency APIs (HPAPI). Leading European and North American API manufacturers say their competitive position in APIs is based on unique technologies and

pharma companies will look at outsourcing to low-cost Asian CMOs rather than to European and North America suppliers as a way of reducing their own costs further, says Peter Young, president of life sciences and chemicals investment banking firm Young and Partners (Y&P; New York). More major pharma companies will announce substantial cost-reduction programs in the year ahead, and that will increase price pressure further on fine chemical suppliers, Young says.

Wages and salaries for chemists in India are 20% of those in the U.S. and Europe, according to API manufacturer Divi's Laboratories (Hyderabad). Indian firms also have a cost advantage in chemical and pharmaceutical manufacturing, says Hari Pujar, chemical engineer and research fellow at Merck Research Laboratories (West Point, PA), a Merck & Co. subsidiary.

Leading U.S.-based CMOs say that even taking into account the cost difference, they can offer a string of benefits to customers that their Indian competitors cannot match. Benefits include proximity to the major U.S. pharma companies and ownership of sophisticated

technologies. Recently, however, and particularly during the past year, Asian firms say they have started to close the gap on all of these assumed advantages, primarily by acquiring established and sometimes poorly performing U.S. custom manufacturers.

Jubilant has acquired a number of pharma research and manufacturing businesses in the past few years, including CRO Target Research Associates (Berkeley Heights, NJ) for \$33.5 million and generics group Trinity Laboratories (Salisbury, MD) for \$12.5 million (*CW*, July 13, 2005, p. 36). Jubilant says that its strategy is bearing fruit with the agreement of manufacturing contracts with multinational life-science companies in 2006 worth a combined \$40 million. The company also has agreed on contract research deals with multinational companies for 2007 worth a combined \$28 million. About 48% of Jubilant's 2005 sales were to European markets, and 25% to the U.S. Jubilant increased profits 41%, to Rs1.1 billion (\$26 million) in the fiscal year ended March 31, 2005, on sales

up 30%, to Rs11.1 billion.

Jubilant's strengthening of its R&D and manufacturing base matches the increased outsourcing demands of multinational companies, the company says. Jubilant has long-standing relationships with more than 150 multinationals, including 15 of the top-20 pharma companies, and seven of the top-10 agchem companies, Shyam S. Bhartia, chairman and managing director of Jubilant, tells *CW*. Expansion into U.S. and European markets has occurred through organic growth and acquisitions, Bhartia says. Jubilant also is involved in drug discovery, and believes its business "has the potential to ramp up significantly over the next few years" in the U.S., he says. The company says it is developing leading-edge custom manufacturing technologies, and that it has unique technologies of its own. "But if there are good opportunities for acquiring new technologies, we would consider such proposals," particularly in the key markets of Europe and the U.S., he adds.



Shaw: Western firms need to be high tech.



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Other Indian CMOs are looking to emulate Jubilant's success through acquisition of custom research and manufacturing companies in Europe and North America. Shasun plans to close the purchase of money-losing RPS by the end of next month (*CW, Jan. 18, p. 25*). The acquisition includes all of RPS's development and custom manufacturing services catering to pharma companies in Asia, Europe, and the U.S., as well as manufacturing sites at Dudley and Annan, U.K. RPS's technologies such as hydrolytic kinetic resolution (HKR), aromatic bond formation (ABF), and Radical Trifluoromethylation, together with their respective patents, are also included, as are products and building blocks related to the technologies.

Shasun generated 60% of its \$73-million sales from Europe and the U.S. in 2004. Buying RPS fits with Shasun's strategy to strengthen its global presence further in API custom synthesis, says CEO Narayanan Govindarajan. "Shasun will be in a better position to serve pharmaceutical industry clients throughout the drug life cycle by offering services for pre-launch, launch, and post-launch supply, as well as for late life cycle," Govindarajan says. The deal will also expand Shasun's customer base across innovator and emerging pharma companies, he says.

NOVEL TECHNOLOGIES. NPIL announced last October that it had agreed to acquire Avecia's pharma business for £9.5 million (\$17 million), in part to secure access to novel technologies in sectors including chiral synthesis, fermentation, biotransformation, and HPAPI production (*CW, Nov. 2, 2005, p. 5*). Avecia's pharma business unit includes API manufacturing activities at Grangemouth and Huddersfield, U.K., and Aurora, ON, and generates sales of £36.1 million/year. The business features "a deep pipeline of products backed by strong customer relationships and a mix of unique technologies," NPIL says. All 350 staff at Avecia Pharmaceuticals will transfer to NPIL. The acquisition provides NPIL with a manufacturing presence in Europe and the U.S., and entry into the HPAPI sector, the company says. NPIL says it had been seeking a suitable acquisition for about one year.

NPIL opted also to acquire Avecia's 25% stake in fine chemical catalyst spin-out Reaxa (Manchester, U.K.), which owns catalyst technologies for fine chemical processing. The

Avecia acquisition follows NPIL's purchase of Rhodia's inhalation anaesthetics business in December 2004.

The Avecia business adds novel technologies to NPIL's low cost base in India. "Avecia Pharmaceuticals has a long tradition of technology-driven, high-end service to the global pharma industry, driven by highly competent specialists," NPIL says. "Additionally, the Avecia business brings a distinct group of new customers from both the big pharma and biotechnology fields." Merging Avecia Pharmaceuticals with NPIL's custom manufacturing group "will go a long way to making the combined entity a truly global custom manufacturing player," says Aja Piramal, chairman of NPIL.



Hiremath: A global player.



Bhartia: Establishing a Western presence.

NPIL says it anticipates that Asian companies will make further acquisitions in Europe and North America. The Avecia Pharmaceuticals deal "will trigger a new wave of restructuring within the global custom manufacturing industry," the company says. "The winning custom manufacturers of the future will have a strong manufacturing base in India with technology and early phase beachheads in North America and Europe," it says. NPIL predicts 2005 after-tax profits of R1.7 billion, on sales of Rs12.3 billion, and says it is a top-four player in the Indian pharma market.

NPIL and several other custom manufacturers in India, say they have each established production deals with overseas pharma companies. NPIL has about \$500 million worth of contracts covering the next eight years for a number of leading pharma companies, including Novartis.

DRL announced last November that it had agreed to purchase Roche's API manufacturing business at Cuernavaca, Mexico for \$59 million, including the cost of working capital (*CW, Nov. 23, 2005, p. 25*). The deal includes all existing business supply contracts, including ongoing supplies to Roche. All 340 of the business's staff will be transferred to DRL.

The former Roche business makes about 18 products including "mature APIs," and a range of intermediates and steroid-based HPAPIs. DRL says the acquisition will enable it to deliver a wider range of pharma services. "Dr Reddys will emerge as a leading player in custom pharmaceutical services, with strategic offerings spanning the entire value chain,"



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says GV Prasad, DRL CEO. DRL is targeting sales of finished products to the U.S., and last year raised \$56 million from ICICI Venture (Bangalore) to fund the launch of generic drugs there. DRL reported a 72% increase in net profits, to Rs890 million, for its fiscal quarter ended September 30, 2005, on sales up 7%, to Rs5.8 billion.

Indian API manufacturer Matrix Laboratories (Secunderabad) has also been acquisitive. In 2005 the company acquired a 43% stake in API and intermediates manufacturer Explora Laboratories (Mendrisio, Switzerland), and a 60% stake in Mchem Group (Xiamen, China), a producer of APIs, basic chemicals, finished-dose products, and intermediates (*CW*, Oct. 12, 2005, p. 33). Matrix also purchased a 22% stake in generics firm Docpharma (Interleuvenlaan, Belgium) in July 2005 for €217 million (\$259 million).

Indian pharma companies are also seeking to acquire small European and U.S. pharma firms. Biocon (Bangalore) has made an approach to acquire the intellectual property of drug developer Nobex (Research Triangle Park, NC) following Nobex's

filing under Chapter 11 bankruptcy protection. Pharma and API manufacturer Sun Pharmaceutical Industries (Mumbai) has made a move to acquire generics firm Able Laboratories (Cranbury, NJ) for \$23 million. Able Laboratories has also filed for chapter 11 due to manufacturing quality issues.

Indian companies are seeking to reduce their own costs by securing deals to source pharma intermediates from Chinese suppliers. Hikal recently announced plans to take a minority stake in a Sinochem fine chemical subsidiary. The move "will help Hikal improve its cost base, as we see many sourcing opportunities of raw materials and intermediates for our APIs," says Jai Hiremath, vice chairman and managing director. "The association with Sinochem will open up new avenues for marketing and sourcing of products in different markets."

Indian generics and API manufacturers are also climbing the technology ladder by licensing in novel processes. Indian companies are among the early adopters of biocatalytic

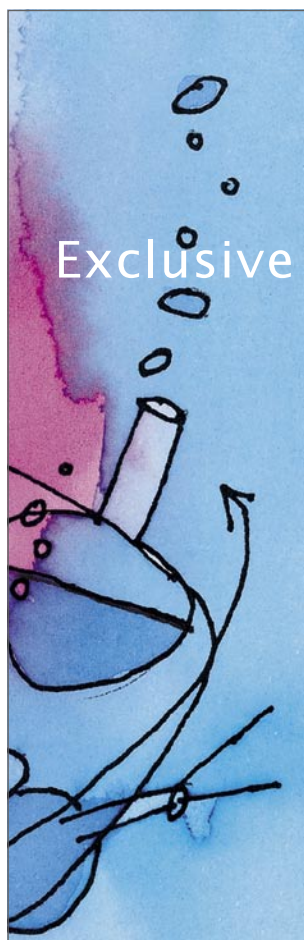
technologies, says Alan Shaw, president and CEO of biocatalysis technology firm Codexis (Redwood City, CA). Codexis says it has agreed on deals to license its proprietary enzyme technology to four Indian firms, including Arch Pharmalabs (Mumbai), Matrix Laboratories, and Shasun, to develop biocatalytic processes using enzymes engineered via Codexis's directed evolution technology.

"Our processes are often as much as 40%-60% cheaper than the nearest chemistry equivalent," Shaw says. Essentially, "you've got a 60% cheaper product than the rest of the market," he says. No additional capital is required as biocatalysts operate in simple, stirred vessels at room temperature, he adds.

Relatively few Europe- or U.S.-based fine chemical firms have entered into agreements with Codexis. "A lot of people in the Western fine chemical industry think they have what they need to be competitive," Shaw says. "The reality is that they haven't. The European and U.S. fine chemical industry has got some real problems here because the only differentiator



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it has left is technology," he adds.

Codexis, in addition to licensing its enzyme technology to third parties, plans to use the technology to produce certain generic APIs, and, using its network of Indian affiliates, to manufacture the products in India. "We are going straight from California to manufacture in India and will be sidestepping production in Europe completely," Shaw says. "This will give a real competitive edge."

Most European and North American API manufacturers have been striving to differentiate themselves from low-cost Asian competitors by developing novel technologies. Firms including Clariant, Lonza, and RPS have also built a manufacturing presence in countries with low labor costs. RPS, has shifted paracetamol capacity from plants in the U.S. and France to Wuxi, China as part of a long-term strategy to reduce costs.

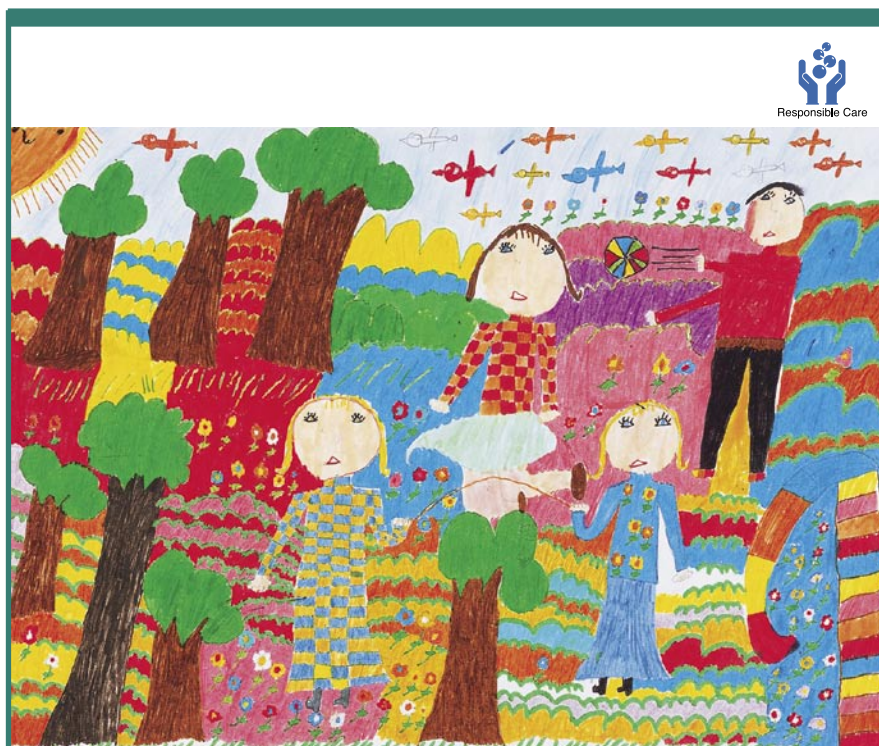
The company also has a cGMP manufacturing facility at Bangpoo, Thailand. RPS's asset base is in "good shape" partly as a result of its low-cost strategy, Nick Green, president of RPS, told *CW* recently. Some pharma companies remain "nervous" about their intellectual property when projects are shifted to Asia, however, Green says. RPS, even prior to its planned purchase by Shasun, provided customers with a choice of production in Asia, North America, or Western Europe, he adds (*CW*, Nov. 16, 2005, p. 23).

Clariant says it is growing its manufacturing base in Asia, and completed construction last year of a Rs80-million (\$1.8 million) intermediates factory at Roha, India that forms part of the company's previously announced plans to shift a significant proportion of its intermediates for agchems and the pharma sector from Europe to countries with low labor costs (*CW*, Jan. 19, 2005, p. 23). The facility provides Clariant with products of international quality at Indian costs, the company says.

Lonza CEO Stefan Bogas announced recently that Lonza is building an R&D center for pharma intermediates and API-related activities at Nansha, China (*CW*, Sept. 21, 2005, p. 42). The center will house about 60 research staff and include research laboratories, process development facilities, and an analytical chemistry facility. It is due to begin operations by the end of this quarter.

ASIAN PARTNERING. Pfizer CentreSource (PCS; Kalamazoo, MI), a Pfizer subsidiary, is taking a different approach. The company tells *CW* that to cut manufacturing costs it plans to partner with Asian contract manufacturers on latter-stage processing of steroid intermediates (*CW*, Feb. 11, p. 22). PCS's technology is based on a single biocatalytic step, which replaces several synthetic chemical steps used during standard manufacture. "As steroid manufacturing has grown in China and elsewhere throughout Asia, we've felt the competitive pressure," says Doris Scheffel Symonds, v.p./global marketing and fine chemicals at PCS. The company says that shifting its technology to Chinese partners in the coming years will give it a competitive edge over any low-cost producer.

CMOs have also been implementing lengthy cost-reduction programs in Europe and the U.S. to ensure they are better able to compete. BASF announced last fall that it would reduce production of caffeine and the cold remedy ingredient pseudoephedrine to reduce costs and improve efficiency at its Minden, Germany operations, in the face of falling demand. DSM has gone a step further,



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announcing recently a major cost-reduction program that involves closing the company's pharma intermediates complex at South Haven, MI in the second quarter of 2007, and mothballing biologic drugs facilities at Montreal (*CW*, Jan. 4/11, p. 31). DSM's actions are expected to generate annualized savings of €20 million from mid-2007, the company says. DSM cites the commoditization of early stage pharma intermediate and

generic API markets that are increasingly served by producers in countries with low labor costs, and by Indian and Chinese companies in particular.

Indian custom manufacturers are also becoming attractive targets for cash-rich pharma companies in other countries. Recent deals include generics firm Watson Pharmaceuticals' (Corona, CA) acquisition of a pharma formulation facility at Verna, India

from DRL. Financial details were not disclosed. Watson, meanwhile, is consolidating its domestic manufacturing base, and within two years says it will close a solid-dose manufacturing facility at Humacao, Puerto Rico.

Generic pharma manufacturer Teva Pharmaceutical Industries (Petach Tikva, Israel) is in talks to acquire bulk drugs, formulations, and oral suspensions producer Aurobindo Pharma (Ameerpet, India), reports say. Both companies declined to comment on the reports.

Foreign API manufacturers may be at a disadvantage when establishing a presence in countries with low labor costs, however, executives say. Many Asian producers flout regulations to avoid costs, unlike European and North American companies that generally adhere to recognized manufacturing-quality standards and waste legislation, they say. And there may be other downsides. "Locating production in a newly developed country opens up liability concerns, not necessarily as a result of an individual plant being out of compliance or of pollution issues, but because of proximity to chemical companies that have lower standards," says Guy Villax, CEO of Hovione.

QUALITY CONCERNS. Villax was closely involved in the recent formation of the European Fine Chemicals Group (EFCG; Brussels), a Cefic lobby group that pressures the European Commission to ensure that drugs imported by Europe from less expensive Asian manufacturers are produced in approved manufacturing plants and under procedures that ensure drug quality. EFCG says sub-quality APIs are entering Europe from plants that have not been inspected by FDA or Europe's equivalent body, the European Medicines Evaluation Agency (EMA).

The European Union introduced legislation last fall to ensure that sub-standard pharmaceutical imports are not permitted in Europe. Senior European fine chemical industry executives are concerned, however, that insufficient funds will be made available to police the legislation (*CW*, July 27, 2004, p. 31). EFCG has published guidelines for European and North American API manufacturers to help strengthen their position. Recommendations include that: API audit reports be no more than three years old; that each producer write and sign a declaration certifying that each API the company supplies is made under GMP requirements as described in Drug Master Files; and that any process changes be notified to the relevant authorities prior to implementation. —ALEX SCOTT

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